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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,575	07/14/2008	Robyn Lynne Ward	037775-0107	4121

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EXAMINER	
SHAW, AMANDA MARIE	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
11/05/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,575	WARD ET AL.	
	Examiner	Art Unit	
	AMANDA SHAW	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,8 and 9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,8 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *4/20/2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/8/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed September 8, 2010. This action is made FINAL.

Claims 1-3, 5, and 8-9 are currently pending.

Claims 1 and 8 have been amended.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on September 8, 2010 has been received. The references listed in the IDS have been reviewed as indicated on the 1449, and a copy is attached herein.

Withdrawn Objections

3. The objection made to the abstract in section 3 of the Office Action of March 12, 2010 is withdrawn in view of the amendments made to the abstract.

The objection made to page 10 of the specification in section 3 of the Office Action of March 12, 2010 is withdrawn in view of the amendments made to the abstract.

Withdrawn Rejections

4. The rejections made under 35 USC 103(a) in sections 6-7 of the Office Action of March 12, 2010 are withdrawn in view of the amendments made to the claims.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following rejection has been modified in response to the amendments:

6. Claims 1-3, 5, and 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Waki (American Journal of Pathology 8/2002 Vol 161 No 2 pages 399-403) in view of Okamoto (Proc. Natl. Acad Sci. 5/1997 Vol 94 pages 5367-5371).

Regarding Claim 1 Waki teaches investigating the promoter methylation status of the hMLH1 and p16 genes. Waki teaches that 94 gastric cancer samples and their

matching non neoplastic gastric tissues were obtained at surgery from 94 patients (page 400, col 1). Thus Waki teaches isolating a population of cells from normal tissue (the non neoplastic gastric tissue) of 94 patients. Waki teaches that genomic DNA was extracted and then the samples were treated with bisulfite and amplified via methylation specific PCR (page 400, col 1). Waki teaches that methylation of hMLH1 and p16 was present in both neoplastic and non neoplastic gastric epithelia as follows: 32% (30 of 94) and 24% (23 of 94) for hMLH1 and 22% (21 of 94) and 44% (41 of 94) for p16 (page 400, col 2). In the instant case both hMLH1 and p16 are associated with gastric cancer since Waki teaches that in gastric cancers the loss of function of hMLH1 and p16 is linked to hypermethylation of CpG islands within their promoters (page 399, col 2). Further it is noted that hMLH1 and p16 are both tumor suppressor genes and both genes are not involved in parental imprinting (not subject to normal parent of origin specific expression). Additionally Waki states that detection of hMLH1 methylation in non neoplastic gastric epithelia may be useful for screening patients who may be at risk of developing gastric cancer (abstract). The phrase "who may be at risk of developing gastric cancer" is being interpreted as meaning that the patients have not already developed gastric cancer (i.e., they are still healthy). Therefore Waki teaches that the risk of gastric cancer in a healthy individual can be assessed by detecting hMLH1 methylation.

Regarding Claim 5 Waki teaches that methylation in the promoter region of hMLH1 correlates well with gene silencing (page 402, col 2). Thus Waki teaches a

method wherein the epimutation (methylation) is present in the promoter region of the hMLH1 gene and is associated with transcriptional silencing of the hMLH1 gene.

Regarding Claim 8 Waki teaches a method wherein the epimutation is present in a gene selected from hMLH1 or p16 (abstract).

Regarding Claim 9 Waki teaches a method wherein the epimutation is present in hMLH1 (abstract).

Waki does not teach a method of quantitatively determining the frequency of epimutation of a particular gene in said population of cells (clm 1). In the instant case this is being interpreted as determining how many cells have the methylated gene in the population of cells. Waki does not teach a method wherein the normal tissue is normal peripheral blood (clms 2 & 3).

However Okamoto teaches a method wherein the methylation status of a part of the H19 promoter was examined in the unaffected adjacent kidney and peripheral blood of Wilms tumor patients to determine whether aberrant methylation of H19 was present in normal tissues (page 5368, col 1). Okamoto teaches that H19 methylation was quantified by determining the percentage of cells with H19 biallelic methylation. This percentage was calculated by using 100(x-1)/(x+1), where x is the methylated H19/unmethylated H19 allele ratio (page 5368, col 1). Thus Okamoto teaches detecting the frequency of epimutation present. Okamoto further teaches that the high proportion of epigenetically modified cells among normal tissues indicates that the epigenetic error occurred very early in development, before the onset of Wilms tumor (abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Waki by quantitatively determining the number of times the hMLH1 and p16 genes are methylated in the population of cells from normal tissue as suggested by Okamoto. In the instant case Okamoto teaches that the high proportion of epigenetically modified cells among normal tissues indicates that the epigenetic error occurred very early in development, before the onset of Wilms tumor (abstract). Waki teaches that detection of hMLH1 methylation in non neoplastic gastric epithelia may be useful for screening patients who may be at risk of developing gastric cancer (abstract). Thus one of skill in the art would have been motivated to determine the frequency of methylation of a particular gene in a population of cells in order to screen patients who may be at risk of developing cancer before the onset of a tumor. Further it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Waki by isolating the population of cells form normal peripheral blood as suggested by Okamoto. In the instant case Okamoto teaches that increased H19 methylation status was detected in one of four blood samples from Wilms tumor patients (page 5368, col 1). As such one of skill in the art would have been motivated to isolate a population of cells from normal peripheral blood in order to achieve benefit of noninvasive detection of cancer. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore the invention as a whole was prima facie obvious to one or ordinary skill in the art at the time the invention was made, as evidenced by the references.

Response to Arguments

7. In the response filed on September 8, 2010 the Applicants traversed the rejections made over Waki in view of Okamoto.

The Applicants argue that key distinction over the cited references is the notion that "risk of cancer" is determined from a healthy individual. The Applicants state that a healthy individual is an individual who has yet to manifest any pathology. They assert that the cited art focuses on individuals who present oncological scintilla (hence, are not "healthy") and on diagnoses concerning the risk that the extant pathology will spread. The Applicants argue that with respect to "non-neoplastic" tissue Waki, indicates that the "risk" of cancer related to MLH1 methylation lies in the fact that carcinogenesis already is underway in the gastric epithelia of the tested subjects. They state that Waki reasons that this phenomenon during aging may be an early warning signal for the beginning of cancer in the gastric epithelia. They argue that Waki's disclosures point to the fact that the prior art method was directed solely to early detection/early signs of disease. They cite Waki for teaches that "results suggest that methylation of hMLH1 in non neoplastic gastric epithelia is pathological and may serve as a useful marker for gastric cancer development". They argue that "pathological" in this context is not normal. In contrast the methodology of the claimed invention is the diagnosis of the risk of disease in a healthy (i.e., non-pathological) tissue.

This argument has been fully considered but is not persuasive. First of all it is noted that the specification has not provided a definition of the word "healthy". Therefore

the examiner may use the broadest reasonable interpretation of the word "healthy" when examining the claims. Waki teaches that detection of hMLH1 methylation in non neoplastic gastric epithelia may be useful for screening patients who may be at risk of developing gastric cancer (abstract). The phrase "who may be at risk of developing gastric cancer" is being interpreted as meaning that the patients have not already developed gastric cancer and therefore they are considered to be healthy individuals. Further it is noted that the specification teaches that "normal tissue" refers to any tissue which is substantially healthy and not showing any significant symptoms or signs of disease (e.g., the tissue is not cancerous). The non neoplastic tissue of Waki is being interpreted as a normal tissue because a non neoplastic tissue sample would not be expected to have abnormal cell proliferation which is a significant sign of cancer.

The Applicants state that another notable feature of the invention resides in its distal nature. They submit that the risk of cancer can be assessed by analyzing normal tissue even though the cancer may manifest in another tissue. They assert that they were the first to described the use of DNA methylation is tissues distal from the tissue affected by a risk of manifesting the disease e.g., assessing the risk of cancer in colon tissue by use of peripheral blood. They argue that Waki only examined the tissue in which the cancer arose (gastric tissue). They argue that when Waki tested other tissues the methylation of hMLH1 was not found in any organ in all age groups except for a non neoplastic lung tissue obtained from a 78 year old male who died of lung cancer. Applicants further argue that Waki teaches away from the use of distal tissue.

This argument has been fully considered but is not persuasive. In the instant case claim 1 requires "isolating a population of cells from normal tissue of said individual". Here it is noted that claims 1, 5, 8, and 9 do not require the normal tissue to be distal tissue. All that is required is that the tissue is normal tissue. In the instant case this is taught by Waki. Specifically Waki teaches isolating a population of cells from normal tissue (the non neoplastic gastric tissue) of 94 patients. As such Waki teaches what is required with respect to claims 1, 5, 8, and 9. Regarding claims 2-3 Applicants are reminded that this is a 103 rejection and an additional reference, Okamoto, has been applied for teaching the concept of detecting methylation in normal peripheral blood. Further Waki does not teach away from using distal tissue. In fact Waki teaches that in a separate study they detected frequent hMLH1 methylation in non neoplastic gastric epithelia not only adjacent to, but also far from each tumor exhibiting a high frequency of microsatellite instability (page 403, col 1).

Regarding Okamoto the Applicants note that the reference deals with Wilms tumor, which involves an imprinted locus, yet the present claims explicitly exclude a method focusing on imprinted genes. They argue for this reason alone the combination of Waki and Okamoto is improper.

This argument has been fully considered but it not persuasive. Okamoto is only being relied upon to teach quantitatively determining the frequency of epimutation of a particular gene in said population of cells and a method wherein the normal tissue is normal peripheral blood. Okamoto is not required to teach a method wherein the tumor suppressor gene is other than one that is subject to normal parent of origin specific

expression because this limitation is taught by Waki. Since both Waki and Okamoto are drawn to methods concerning detecting methylation they are considered to be compatible references.

Additionally the Applicants argue that Okamoto teaches away from the use of distal tissue. The Applicants assert that Okamoto focuses on the tissue in which the cancer arose. They state that Okamoto examined peripheral blood yet Okamoto does not correlate the methylation status in peripheral blood with the risk of Wilms tumor. They note that increased H19 methylation was detected in only one of four patients have tumors. They argue that Okomoto would afford a correct risk analysis in relation to applicants claimed methodology only 25% of the time from a population that should be 100% positive.

This argument has been fully considered but is not persuasive. In the instant case claims 1, 5, 8, and 9 do not require the normal tissue to be distal tissue. The use of peripheral blood is only required by claims 2-3. Okamoto teaches a method wherein the methylation status of a part of the H19 promoter was examined in the unaffected adjacent kidney and peripheral blood of Wilms tumor patients to determine whether aberrant methylation of H19 was present in normal tissues (page 5368, col 1). As such Okamoto teaches a method wherein the normal tissue is normal peripheral blood. Okamoto further teaches that the high proportion of epigenetically modified cells among normal tissues (which includes the peripheral blood) indicates that the epigenetic error occurred very early in development, before the onset of Wilms tumor (abstract). The argument that the claimed methodology would work only 25% of the time is not

persuasive because the claims do not require being able to assess the risk of cancer with any particular level of accuracy. For these reasons the rejections are maintained.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

/Stephen Kapushoc/

Primary Examiner, Art Unit 1634